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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/693,754	10/20/2000	Neil Berinstein	13115	7885

7590 12/17/2003

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EXAMINER

WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 12/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/693,754

Applicant(s)

BERINSTEIN ET AL.

Examiner

Anne Marie S. Wehbe

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 September 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2 and 4-28 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2 and 4-28 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

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DETAILED ACTION

Applicant's amendment filed on 9/5/03 has been entered. Claim 3 has been canceled and new claims 20-28 have been added. Claims 1-2, and 4-28 are pending in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in the instant action can be found in the previous office action.

Regarding applicant's request that the applicant's docket number be changed, please note that the Office identifies cases by their U.S. Patent Application Number. The Office does not keep track of attorney docket numbers. The attorney of record is free to change his/her own docket number as it appears on communications with the Office.

As requested, copies of the signed 1149s received on 11/1/01 and 2/5/02 are attached to the instant office action.

Claim Rejections - 35 USC § 112

The rejection of claims 4-16 under 35 U.S.C. 112, second paragraph, for indefiniteness is withdrawn in view of applicant's amendments to claim 4.

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Claim Rejections - 35 USC § 102

The rejection of claims 1-4, 9-10, and 16-17 under 35 U.S.C. 102(a) as being anticipated by WO 99/30733, 6/24/99, hereafter referred to as Dalemans et al., is withdrawn in view of applicant's amendments to the claims.

Claim Rejections - 35 USC § 103

The rejection of claims 1-2, 4-14, and 16-17 under 35 U.S.C. 103(a) as being unpatentable over Hurpin et al. (1998) Vaccine, Vol. 16 (2/3) 208-215, in view of Hodge et al. (1997) Vaccine, Vol. 15, No. 6/7, 759-768, is withdrawn in view of applicant's amendments to the claims.

The rejection of claims 1, and 17-19 under 35 U.S.C. 103(a) as being unpatentable over Hurpin et al. (1998) Vaccine, Vol. 16 (2/3) 208-215, in view of Hodge et al. (1997) Vaccine, Vol. 15, No. 6/7, 759-768, as applied to claims 1-2, 4-14, and 16-17 above, and further in view of Zaremba et al. (1997) Canc. Res., Vol. 57, 4570-4577 and Salgaller et al. (1996) Canc. Res., Vol. 56, 4749-4757, is withdrawn in view of applicant's amendments to the claims.

Applicant's amendments to the claims and addition of new claims 20-28 have necessitated the following new grounds of rejection.

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Claims 1-2, 4-17, and 20 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Hurpin et al. (1998) Vaccine, Vol. 16 (2/3) 208-215, in view of Hodge et al. (1997) Vaccine, Vol. 15, No. 6/7, 759-768, and Lehner et al. (1999) J. Infect. Dis., Vol. 179 (Suppl 3), S489-S492. The applicant claims methods of inducing an immune response to a tumor antigen in an animal comprising a priming step wherein a tumor antigen is administered in a first form to a lymphatic site, and a boosting step wherein the tumor antigen is administered in a second form to a lymphatic site, wherein at least one or both of said forms is administered into a lymph node. The applicant further claims said methods wherein the tumor antigen is selected from a group which includes p53 and wherein the tumor antigen is in the form of a nucleic acid selected from a group which includes the canarypox nucleic acid, ALVAC.

Hurpin et al. teaches the generation of anti-53 CTL responses in mice following intrasplenic injection of ALVAC encoding p53 (Hurpin et al., page 209, column 2, second paragraph, and page 210, column 2, last paragraph, and page 211, Figure 1, panel b). While Hurpin et al. does not specifically teach a boosting step in addition to a priming step, Hurpin et al. does teach that the route of administration is also important for boosting the response (Hurpin et al., page 211, column 1, paragraph 1). Hodge et al. supplements Hurpin et al. by teaching a diversified prime and boost protocol for enhancing T-cell immunity and antitumor immune responses. Specifically, Hodge et al. teaches that priming an anti-tumor immune response by administering a vaccinia virus encoding CEA followed by boosting with an avipox virus (ALVAC) encoding CEA results in the generation of anti-CEA immune responses superior to those generated by the use of either vector alone (Hodge et al., page 759, and page 766, Table 3).

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Please note that Vaccinia virus encoding CEA and ALVAC encoding CEA represent different forms of the same tumor antigen since vaccinia is a cowpox virus and ALVAC is an avipox virus.

While Hurpin et al. teaches the administration of the tumor antigen to a lymphatic site, the spleen, neither Hurpin et al. nor Hodge et al. specifically teaches the administration of the antigen to the lymph node. Lehner et al. supplements Hurpin et al. and Hodge et al. by teaching that the route of administration can have profound effects on the immune response. Specifically, Lehner et al. showed that a direct comparison of intramuscular versus intradermal versus targeted iliac lymph node immunization revealed that targeted iliac lymph node administration of antigen resulted in increased T and B cell mediated antigen-specific immune responses (Lehner et al., page S489, and page S491). Thus, by demonstrating that administration of antigen to the iliac lymph node results in increased T and B cell mediated antigen-specific immune responses over other routes of administration, Lehner et al. provides motivation for substituting intranodal administration over the intrasplenic or intramuscular administration routes taught by Hurpin et al. and Hodge et al.

Based on the motivation to use a diversified prime and boost strategy as taught by Hodge et al., the motivation to utilize lymphatic administration for generating CTL using ALVAC encoding tumor antigens as taught by Hurpin et al., and the motivation for specifically use iliac lymph node administration to maximize immune responses as taught by Lehner et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to administer a vaccinia virus encoding a tumor antigen, either CEA or p53, to a lymphatic site, and particularly the lymph nodes, followed by the intrasplenic or intranodal administration of an avipox vector encoding

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either CEA or p53 in order to induce an immune response in an animal. Further, based on the successful use of intrasplenic and intranodal administration to generate antigen specific T and B cell responses as taught by Hurpin et al., and Lehner et al., and the successful use of a second vector to boost the immune response taught by Hodge, the skilled artisan would have had a reasonable expectation of success in inducing an immune response in an animal by intranodal administration of a vaccinia virus encoding a tumor antigen, either CEA or p53, followed by the intranodal administration of an avipox vector encoding either CEA or p53.

Applicant's arguments concerning the teachings of Hurpin et al. and Hodge et al. are addressed as they pertain to the instant grounds of rejection. The applicant argues that neither Hurpin et al. nor Hodge et al. teaches the administration of the antigen to the lymph node. However, in the instant rejection of record, Lehner et al. supplies the teachings and motivation to use intranodal administration of an antigen. Therefore, applicant's arguments regarding the teachings of Hurpin et al. and Hodge et al. have not been found persuasive in overcoming the instant grounds of rejection of the claims.

Claims 18-19 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Hurpin et al. (1998) Vaccine, Vol. 16 (2/3) 208-215, in view of Hodge et al. (1997) Vaccine, Vol. 15, No. 6/7, 759-768, and Lehner et al. (1999) J. Infect. Dis., Vol. 179 (Suppl 3), S489-S492, as applied to claims 1-2, 4-17, and 20 above, and further in view of Zaremba et al. (1997) Canc. Res., Vol. 57, 4570-4577 and Salgaller et al. (1996) Canc. Res., Vol. 56, 4749-4757. The applicant claims methods of inducing an immune response to a tumor antigen in an animal

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comprising a priming step wherein a tumor antigen is administered in a first form to a lymphatic site, and a boosting step wherein the tumor antigen is administered in a second form to a lymphatic site, wherein either one or both of the lymphatic sites is a lymph node. The applicant further claims said methods wherein the tumor antigen comprises the sequence YLSGADLNL or YLEPGPVTV.

The combined teachings of Hurpin et al. in view of Hodge et al. and Lehner et al., as discussed in detail above, provide motivation for the use of a diversified prime and boost strategy which utilizes intranodal injection of a vaccinia virus encoding a tumor antigen, such as CEA or p53, followed by the intranodal administration of an avipox vector encoding a tumor antigen in order to induce an immune response in an animal. While Hurpin et al. and Hodge et al. teach the generation of anti-tumor immune responses against tumor antigens, including CEA, neither Hurpin et al. nor Hodge et al. teach wherein the tumor antigen comprises the sequence YLSGADLNL or YLEPGPVTV.

Zaremba et al. supplements Hurpin and Hodge by teaching that the YLSGADLNL epitope is a CTL enhancer agonist peptide for inducing potent anti-CEA CTL (Zaremba et al., page 4570, abstract). Zaremba et al. further provides motivation for using the modified CEA peptide to induce anti-CEA CTL by teaching that the YLSGADLNL peptide is more potent than the unmodified YLSGANLNL peptide in inducing anti-CEA CTL (Zaremba et al., page 4574). Sangeller et al. further supplements Hurpin and Hodge by teaching a modified gp100 peptide YLEPGPVTV, which also demonstrates an enhanced ability to generate anti-gp100 CTL than the unmodified YLEPGPVTA peptide (Sangeller et al., page 4749, abstract and column 2). Thus,

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based on the motivation provided by Zaremba et al. and Sangeller et al. that the modified peptides YLSGADLNL and YLEPGPVTV are more potent than the unmodified parent peptides at generating anti-CEA or anti-gp100 CTL respectively, it would have been *prima facie* obvious to the skilled artisan at the time of filing to substitute the modified YLSGADLNL or YLEPGPVTV peptides for the unmodified tumor antigens taught by Hurpin and Hodge, and further to use those peptides in the methods of Hurpin et al. in view of Hodge et al. and Lehner et al. for immunizing a mammal with a reasonable expectation of success.

Claims 21-28 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Hurpin et al. (1998) Vaccine, Vol. 16 (2/3) 208-215, in view of Hodge et al. (1997) Vaccine, Vol. 15, No. 6/7, 759-768, and Lehner et al. (1999) J. Infect. Dis., Vol. 179 (Suppl 3), S489-S492, as applied to claims 1-2, 4-17, and 20 above, and further in view of Barnett et al. (1997) Vaccine, Vol. 15(8), 869-873. The applicant claims methods of inducing an immune response to a tumor antigen in an animal comprising a priming step wherein a tumor antigen is administered in a first form to a lymphatic site, and a boosting step wherein the tumor antigen is administered in a second form to a lymphatic site, wherein either one or both of the lymphatic sites is a lymph node. The applicant further claims said methods wherein the first form is a nucleic acid and the second form in a peptide.

The combined teachings of Hurpin et al. in view of Hodge et al. and Lehner et al., as discussed in detail above, provide motivation for the use of a diversified prime and boost strategy which utilizes intranodal injection of a vaccinia virus encoding a tumor antigen, such as CEA or

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p53, followed by the intranodal administration of an avipox vector encoding a tumor antigen in order to induce an immune response in an animal. Although Hurpin et al. and Hodge et al. teach immunization using a nucleic acid encoding the tumor antigen in the form of a recombinant virus, neither reference teaches boosting the immune response from a nucleic acid immunization with a peptide.

Barnett et al. supplements Hurpin et al., Hodge et al., and Lehner et al., by teaching a prime/boost vaccination strategy which includes a priming step with a nucleic acid encoding an antigen and a boosting step with a protein form of the antigen (Barnett et al., page 869-870). Barnett et al. also teaches that the nucleic acid form of the antigen can be a plasmid DNA vector or recombinant canarypox virus (Barnett et al., page 869, and page 872, column 2, last paragraph). Barnett et al. further provides motivation for including a boosting immunization with polypeptide antigen following recombinant nucleic acid immunization by demonstrating that animals vaccinated using the prime/boost strategy had significantly increase T and B cell responses than animals which received the nucleic acid alone (Barnett et al., page 869, and page 871).

Therefore, based on the motivation for boosting nucleic acid based immunization with the administration of polypeptide antigen provided by Barnett et al., and in view of the motivation provided by Hodge et al. for prime/boost immunization using two different recombinant viruses, it would have been *prima facie* obvious at the time of filing to use utilize the prime/boost strategy of either Hodge et al. or Barnett et al. in order to increase antigen specific T and B cell responses in an animal. Further, based on the successful demonstration by Barnett et al. that boosting with

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polypeptide antigen increases antigen specific immune responses, the skilled artisan would have had a reasonable expectation of success in generating anti-tumor antigen specific immune responses *in vivo* by priming with a nucleic acid such as a plasmid or recombinant canarypox virus encoding a tumor antigen and boosting with a polypeptide form of the antigen.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's

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supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 872-9306.

Please note that the United States Patent and Trademark Office will begin to move to the new campus in Alexandria, Virginia, in December 2003. The examiners of Art Unit 1632 will be moving in January 2004. As of January 13, 2004, this examiner's phone number will be (571) 272-0737, and that of the examiner's supervisor will be (571) 272-0734.

Dr. A.M.S. Wehbé

ANNE M. WEHBE PH.D
PRIMARY EXAMINER

